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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,952	08/17/2000	Michael S. Kinch	3220-66872	3252

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/640,952	KINCH ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3-13,21,23,24,33,36,37,41-47,49-56,59-68,72,73,75-77,92-94 and 96-101* is/are allowed.

6)☒ Claim(s) *69, 78-81, 90, 91, 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,3-13,21,23,24,33,36,37,41-47,49-56,59-69,72,73,75-81 and 90-101.

DETAILED ACTION

1. Claims 1, 4, 21, 24, 47, 50, 54, 68, 69, 77, 81, 90 and 91 have been amended. Claims 28, 30, 34, 35, 57 and 58 have been canceled. Claims 92-101 have been added. Claims 1, 3-13, 21, 23, 24, 33, 36, 37, 41-47, 49-56, 59-69, 72, 73, 75-81, 90-101 are pending and under consideration.

2. Sections of Title 35, U.S. Code not found in this action can be found in a prior action.

3. Claim78-81 and 95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 78 and 95 lack an active method step correlating the assay for EphA2 intracellular localization and phosphorylation with the determination of the disease stage of the cancer cells.

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 78-81 and 95 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The instant claims are drawn to the determination of the disease stage in a cell population. Without an active method step linking the assay of EphA2 localization and phosphorylation with the determination of the disease stage, the method reads on a cognitive process for determining the disease stage because there is no correlation between the outcome of the assay and the final method step of determining the disease stage.

6. Claims 90 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Easty et al (International Journal of Cancer, 1995, vol. 60, pp. 129-136) as evidenced by the abstract of Chen et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 24670-24675) and Lindberg et

al (Molecular and Cellular biology, 1990, vol. 10, pp. 6316-6324) in view of Larrick et al (In: Human Hybridomas and Monoclonal Antibodies, Engleman and Foung, Ed.s, 1985, pp. 8-9).

Claim 90 is drawn in part to a method for detecting the presence of cancer cells in a selected cell population comprising assaying at least a portion of the selected cell population for a change in EphA2 expression level as compared to EphA2 expression level in an analogous normal cell population, wherein he assaying the cell population comprises incubating at least a portion of the selected cell population with a monoclonal antibody and wherein the change is indicative of the presence of cancer cells in the selected cell population. Claim 91 embodies the method of claim 90 wherein the change in EphA2 expression level is indicative of the presence of non-metastatic cells in the cell population.

The abstract of Chen et al discloses that EphA2 is synonymous with Eck.

Easty et al teach a method for detecting metastatic melanoma cells in a cell population comprising the steps of lysing at least a portion of the cell population, incubating the lysed cells with a polyclonal antibody that specifically binds to Eck to allow antibody binding to Eck and detecting antibody-Eck binding by Western blot methodology using chemiluminescence as a detectable label (page 131, under the heading "Immunoblotting analysis"). Easty et al teach that an anti-Eck antibody was prepared by the method of Lindberg et al (Molecular and Cellular Biology, 1990, Vol. 10, pp. 6316-6324). Lindberg et al teach that antibodies were raised to the Eck protein by means of a fusion protein comprising residues 874 to 974 of Eck which are the 101 amino acids at the C-terminus (page 6321, first column, lines 4-7 under the heading "Eck has in vitro kinase activity and autophosphorylates on tyrosine residues") and is an intracellular portion of Eck (figure 1 and page 6319, first column, lines 9-13 under the heading "eck encodes a new receptor PTK in the eph/elk family" and figure 3). Lindberg et al also teach that an anti-Eck antibody was made by binding to anti-Eck antibodies that bound to an Eck fusion protein as described by Lindberg et al. Thus, it is inherent in the method of Easty et al that the anti-Eck antibody bound to an intracellular epitope of Eck. Easty et al teach that elevated expression of Eck appeared to be correlated with metastasis to epithelial sites such as lung and ileum, rather than to non-epithelial sites such as lymph nodes and cutaneous deposits (page 132, second column, lines 14-19), thus fulfilling the specific embodiments of cell populations comprising lung, colon and epithelial cells. Easty et al teach the detection of Eck protein by means of a

polyclonal antiserum specific for Eck (page 131, first column, lines 10-12). The antiserum referenced by Easty et al was made by Lindberg et al against a fusion protein comprising amino acids 874-974 of Eck which comprises an intracellular domain of Eck. Easty et al do not teach the detection of metastatic melanoma cells using a monoclonal anti-Eck antibody.

Larrick et al teach the advantages of using a monoclonal antibody over a polyclonal antibody which include a constant propagating source (pages 7-8, under the heading IV).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to make a monoclonal antibody that binds to amino acids 874-974 of Eck. One of skill in the art would have been motivated to do so by the teachings of Larrick et al on the convenience and predictability of monoclonal antibodies versus polyclonal serum.

7. Claims 69, 90 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Easty et al (International Journal of Cancer, 1995, vol. 60, pp. 129-136) and the abstract of Chen et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 24670-24675) and Lindberg et al (Molecular and Cellular biology, 1990, vol. 10, pp. 6316-6324) and Larrick et al (In: Human Hybridomas and Monoclonal Antibodies, Engleman and Foung, Ed.s, 1985, pp. 8-9) as applied to claims 90 and 91 above and in further view of Easty et al (International Journal of Cancer, 1997, Vol. 71, pp. 1061-1065).

Claim 69 is drawn to a method for detecting the presence of metastatic cells in a cell population comprising incubating at least a portion of the cell population with a first antibody that specifically binds to EphA2 to allow binding of the antibody to EphA2 detecting antibody-EphA2 binding, incubating the portion of the cell population with a second antibody having phosphotyrosine specificity and observing the level of binding of the second antibody to cells in the cell population, wherein the presence of metastatic cells in the cell population is indicated by an alteration in binding of one or both of the first or second antibodies compared to the binding of said first of second antibodies to cells in an analogous normal cell population.

Easty et al (1997) teaches that in addition to Eck, other protein tyrosine kinases are ectopically expressed in melanoma include Her2, Fgf-R4, Hek2, Tie, Tyro-9 and 10 and Axel (page 1061, first column, second full paragraph under the abstract, and title). Easty et al teach that the expression of the tyrosine kinases Ptk7 and Sek is lost in malignant melanoma. and that

the expression of Kit and Tyro-3 is also decreased during melanoma progression but that Kdr and Met can be either increased or decreased in melanomas (page 1061, second column, lines 5-12).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to use an antibody which would specifically bind another protein tyrosine kinase that was known to be ectopically expressed in malignant melanoma. or was known to have lost expression in malignant melanoma. One of skill in the art would have been motivated to do so by the teachings of Easty et al (1997) which indicate that the measurement of a single protein tyrosine kinase does not provide an absolute correlation with malignancy because while the trend is loss of tyrosine kinase expression, some tyrosine kinases are over expressed in some cell lines and lost in other cells lines (page 1061, second column, lines 5-12). Thus, one of skill in the art would be motivated to measure the expression of more than one tyrosine kinase known to be ectopically expressed, lost or over expressed in malignant melanoma.

8. All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants amendments.

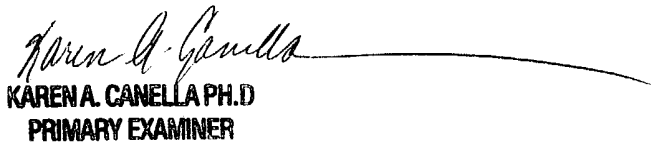
9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

12/13/2004



KAREN A. CANELLA PH.D
PRIMARY EXAMINER